


WEST Search History

DATE: Thursday, February 03, 2005

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	<i>DB=USPT; PLUR=YES; OP=AND</i>		
<input type="checkbox"/>	L1	5880141.pn.	1
<input type="checkbox"/>	L2	L1 and (raf or cak or cad or cadtk or pyk or pyk2 or pyk-2 or ca or raftk)	1
<input type="checkbox"/>	L3	\$indoline or \$indolinone	7886
<input type="checkbox"/>	L4	L3 and (raf or cak or cad or cadtk or pyk or pyk2 or pyk-2 or ca or raftk)	2927
<input type="checkbox"/>	L5	L4 and kinase	243
<input type="checkbox"/>	L6	L5 and tyrosine	174
<input type="checkbox"/>	L7	L5 and \$tyrosine	174
<input type="checkbox"/>	L8	modulate or modulator or modulation or regulate or regulator or regulation or inactivate or inactivator or inactivation or agonist or antagonist or inhibit or inhibitor or inhibition or block or blocks or blocking or blocked or blocker	1579503
<input type="checkbox"/>	L9	L8 same l3	396
<input type="checkbox"/>	L10	L9 and l7	84
<input type="checkbox"/>	L11	l10 and pyk2	18
<input type="checkbox"/>	L12	sugen.asn. and (method or process).clm.	98
<input type="checkbox"/>	L13	L12 and l8.clm.	40
<input type="checkbox"/>	L14	L13 not l11	33

search notes

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Swiss-

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Q14289

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[\[Features\]](#) [\[Sequence\]](#) [\[Tools\]](#)

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Entry information

Entry name **FAK2_HUMAN**
 Primary accession number **Q14289**
 Secondary accession numbers **Q13475 Q14290 Q16709**
 Entered in Swiss-Prot in **Release 36, July 1998**
 Sequence was last modified in **Release 36, July 1998**
 Annotations were last modified in **Release 46, February 2005**

Name and origin of the protein

Protein name **Protein tyrosine kinase 2 beta**
 Synonyms **EC 2.7.1.112**
Focal adhesion kinase 2
FADK 2
Proline-rich tyrosine kinase 2
Cell adhesion kinase beta
CAK beta
Calcium-dependent tyrosine kinase
CADTK
Related adhesion focal tyrosine kinase

Gene name **Name: PTK2B**
 Synonyms: FAK2, PYK2, RAFTK

From **Homo sapiens (Human) [TaxID: 9606]**

Taxonomy **Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.**

References

- [1] NUCLEOTIDE SEQUENCE (ISOFORM 1).
 TISSUE=Brain;
 DOI=10.1038/376737a0;MEDLINE=95379967;PubMed=7544443 [NCBI, ExPASy, EBI, Israel, Japan]
 Lev S., Moreno H., Martinez R., Canoll P., Peles E., Musacchio J.M., Plowman G.D., Rudy B., Schlessinger J.;

"Protein tyrosine kinase PYK2 involved in Ca(2+)-induced regulation of ion channel and MAP kinase functions.";
Nature 376:737-745(1995).

[2] NUCLEOTIDE SEQUENCE (ISOFORM 1).

TISSUE=Hippocampus;

DOI=10.1006/geno.1996.0149;MEDLINE=96435932;PubMed=8838818 [NCBI, ExPASy, EBI, Israel, Japan]

Herzog H., Nicholl J., Hort Y.J., Sutherland G.R., Shine J.;

"Molecular cloning and assignment of FAK2, a novel human focal adhesion kinase, to 8p11.2-p22 by nonisotopic in situ hybridization.";

Genomics 32:484-486(1996).

[3] NUCLEOTIDE SEQUENCE (ISOFORM 1).

TISSUE=Hippocampus;

DOI=10.1074/jbc.270.36.21206;MEDLINE=95403356;PubMed=7673154 [NCBI, ExPASy, EBI, Israel, Japan]

Sasaki H., Nagura K., Ishino M., Tobioka H., Kotani K., Sasaki T.;

"Cloning and characterization of cell adhesion kinase beta, a novel protein-tyrosine kinase of the focal adhesion kinase subfamily.";

J. Biol. Chem. 270:21206-21219(1995).

[4] NUCLEOTIDE SEQUENCE (ISOFORM 1).

DOI=10.1074/jbc.270.46.27742;MEDLINE=96070905;PubMed=7499242 [NCBI, ExPASy, EBI, Israel, Japan]

Avraham S., London R., Fu Y., Ota S., Hiregowdara D., Li J., Jiang S., Pasztor L.M., White R.A., Groopman J.E., Avraham H.;

"Identification and characterization of a novel related adhesion focal tyrosine kinase (RAFTK) from megakaryocytes and brain.";

J. Biol. Chem. 270:27742-27751(1995).

[5] NUCLEOTIDE SEQUENCE (ISOFORM 2).

TISSUE=Monocytes;

DOI=10.1074/jbc.273.16.9361;MEDLINE=98211954;PubMed=9545257 [NCBI, ExPASy, EBI, Israel, Japan]

Li X., Hunter D., Morris J., Haskill J.S., Earp H.S.;

"A calcium-dependent tyrosine kinase splice variant in human monocytes. Activation by a two-stage process involving adherence and a subsequent intracellular signal.";

J. Biol. Chem. 273:9361-9364(1998).

[6] NUCLEOTIDE SEQUENCE.


Blechs Schmidt K., Jandrig B., Baumgart C., Dette M.D., Jahn N., Menzel U., Schilhabel M.B., Wen G., Taudien S., Rosenthal A.;

Submitted (OCT-2000) to the EMBL/GenBank/DDBJ databases.

[7] NUCLEOTIDE SEQUENCE (ISOFORM 1).

TISSUE=Lymph;

DOI=10.1073/pnas.242603899;MEDLINE=22388257;PubMed=12477932 [NCBI, ExPASy, EBI, Israel, Japan]

Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G., Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D., Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K., Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., , Marra M.A.;

"Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences.";

Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).

[8] INTERACTION WITH DDEF2.

PubMed=10022920 [NCBI, ExPASy, EBI, Israel, Japan]

Andreev J., Simon J.-P., Sabatini D.D., Kam J., Plowman G., Randazzo P.A., Schlessinger J.;
 "Identification of a new Pyk2 target protein with Arf-GAP activity.";
 Mol. Cell. Biol. 19:2338-2350(1999).

[9] PHOSPHORYLATION SITE TYR-402, MUTAGENESIS OF PRO-859, AND INTERACTION WITH NEPHROCYSTIN.

DOI=10.1073/pnas.171269898;MEDLINE=21396557;PubMed=11493697 [NCBI, ExPASy, EBI, Israel, Japan]

Benzing T., Gerke P., Hoepker K., Hildebrandt F., Kim E., Walz G.;
 "Nephrocystin interacts with Pyk2, p130(Cas), and tensin and triggers phosphorylation of Pyk2.";
 Proc. Natl. Acad. Sci. U.S.A. 98:9784-9789(2001).

[10] PHOSPHORYLATION SITES TYR-579 AND TYR-580.

DOI=10.1073/pnas.2436191100;PubMed=12522270 [NCBI, ExPASy, EBI, Israel, Japan]

Salomon A.R., Ficarro S.B., Brill L.M., Brinker A., Phung Q.T., Ericson C., Sauer K., Brock A., Horn D.M., Schultz P.G., Peters E.C.;
 "Profiling of tyrosine phosphorylation pathways in human cells using mass spectrometry.";
 Proc. Natl. Acad. Sci. U.S.A. 100:443-448(2003).

Comments

- **FUNCTION:** Involved in calcium induced regulation of ion channel and activation of the map kinase signaling pathway. May represent an important signaling intermediate between neuropeptide activated receptors or neurotransmitters that increase calcium flux and the downstream signals that regulate neuronal activity. Interacts with the SH2 domain of Grb2. May phosphorylate the voltage-gated potassium channel protein Kv1.2. Its activation is highly correlated with the stimulation of c-Jun N-terminal kinase activity.
- **CATALYTIC ACTIVITY:** ATP + a protein tyrosine = ADP + a protein tyrosine phosphate.
- **SUBUNIT:** Interacts with Crk-associated substrate (Cas), PTPNS1 (*By similarity*), Nephrocystin, DDEF2 and OPHN1L.
- **SUBCELLULAR LOCATION:** Cytoplasmic. Interaction with Nephrocystin induces the membrane-association of the kinase.
- **ALTERNATIVE PRODUCTS:**
 - Alternative splicing [2 named forms] Display all isoform sequences in FASTA format

Name 1

Isoform ID Q14289-1

This is the isoform sequence displayed in this entry.

Name 2

Isoform ID Q14289-2

Features which should be applied to build the isoform sequence: VSP_004981.

- **TISSUE SPECIFICITY:** Most abundant in the brain, with highest levels in amygdala and hippocampus. Low levels in kidney. Also expressed in spleen and lymphocytes.
- **PTM:** Phosphorylated on tyrosine residues in response to various stimuli that elevate the intracellular calcium concentration, as well as by PKC activation. Recruitment by Nephrocystin to cell matrix adhesions initiates Tyr-402 phosphorylation. In monocytes, adherence to substrata is required for tyrosine phosphorylation and kinase activation. Angiotensin II, thapsigargin and L-alpha-lysophosphatidic acid (LPA) also induce autophosphorylation and increase kinase activity (*By similarity*).
- **SIMILARITY:** Belongs to the Tyr protein kinase family. FAK subfamily.
- **SIMILARITY:** Contains 1 FERM domain.

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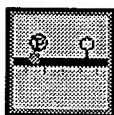
Cross-references

EMBL	U33284; AAC50203.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	L49207; AAB47217.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	D45853; BAA08289.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	U43522; AAC05330.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	S80542; AAB35701.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	AF311103; -; NOT_ANNOTATED_CDS. BC042599; AAH42599.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
PIR	S60248; S60248.	
HSSP	Q05397; 1K04. [HSSP ENTRY / PDB]	
Ensembl	ENSG00000120899; Homo sapiens. [Contig view]	
Genew	HGNC:9612; PTK2B.	
CleanEx	HGNC:9612; PTK2B.	
GeneCards	PTK2B.	
GeneLynx	PTK2B; Homo sapiens.	
GenAtlas	PTK2B.	
MIM	601212 [NCBI / EBI].	
GO	GO:0005737; Cellular component: cytoplasm (<i>traceable author statement</i>).	
	GO:0004715; Molecular function: non-membrane spanning protein tyrosine kinase activity (<i>traceable author statement</i>).	
	GO:0004871; Molecular function: signal transducer activity (<i>non-traceable author statement</i>).	
	GO:0006915; Biological process: apoptosis (<i>traceable author statement</i>).	
	GO:0008284; Biological process: positive regulation of cell proliferation (<i>traceable author statement</i>).	
	GO:0006468; Biological process: protein amino acid phosphorylation (<i>traceable author statement</i>).	
	GO:0006461; Biological process: protein complex assembly (<i>traceable author statement</i>).	
GO	GO:0006950; Biological process: response to stress (<i>traceable author statement</i>).	
	GO:0007172; Biological process: signal complex formation (<i>traceable author statement</i>).	
	GO:0007165; Biological process: signal transduction (<i>traceable author statement</i>).	
	QuickGo view.	
SOURCE	PTK2B; Homo sapiens.	
	IPR000299; Band_4.1.	

InterPro IPR009065; FERM.
 IPR005189; Focal_AT.
 IPR011009; Kinase_like.
 IPR000719; Prot_kinase.
 IPR001245; Tyr_pkinase.
 IPR008266; Tyr_pkinase_AS.
 Graphical view of domain structure.
 Pfam PF03623; Focal_AT; 1.
 PF00069; Pkinase; 1.
 Pfam graphical view of domain structure.
 PRINTS PR00109; TYRKINASE.
 ProDom PD000001; Prot_kinase; 1.
 [Domain structure / List of seq. sharing at least 1 domain]
 SMART SM00295; B41; 1.
 SM00219; TyrKc; 1.
 PS00660; FERM_1; FALSE_NEG.
 PS00661; FERM_2; FALSE_NEG.
 PS50057; FERM_3; 1.
 PROSITE PS00107; PROTEIN_KINASE_ATP; 1.
 PS50011; PROTEIN_KINASE_DOM; 1.
 PS00109; PROTEIN_KINASE_TYR; 1.
 PROSITE graphical view of domain structure.
 HOVERGEN [Family / Alignment / Tree]
 BLOCKS Q14289.
 ProtoNet Q14289.
 ProtoMap Q14289.
 PRESAGE Q14289.
 DIP Q14289.
 ModBase Q14289.
 SMR Q14289; 420B21046274E7C2.
 SWISS-2DPAGE Get region on 2D PAGE.
 UniRef View cluster of proteins with at least 50% / 90% identity.

Keywords

Alternative splicing; ATP-binding; Phosphorylation; Polymorphism; Transferase; Tyrosine-protein kinase.

Features

Feature table viewer



Feature aligner

Key	From	To	Length	Description	FTId
DOMAIN	39	359	321	FERM.	
DOMAIN	425	683	259	Protein kinase.	
NP_BIND	431	439	9	ATP (By similarity).	
BINDING	457	457		ATP (By similarity).	
ACT_SITE	549	549		Proton acceptor (By similarity).	
DOMAIN	702	767	66	Pro-rich.	

DOMAIN	831	869	39	Pro-rich.	
DOMAIN	868	1009	142	Focal adhesion targeting (FAT).	
MOD_RES	402	402		Phosphotyrosine.	
MOD_RES	579	579		Phosphotyrosine (by autocatalysis).	
MOD_RES	580	580		Phosphotyrosine.	
MOD_RES	881	881		Phosphotyrosine (<i>By similarity</i>).	
VARSPLIC	739	780		Missing (in isoform 2).	VSP_004981
VARIANT	838	838	*	K -> T (in dbSNP:751019) [NCBI/Ensembl].	VAR_020284
MUTAGEN	859	859		P->A: Loss of interaction with nephrocystin.	
CONFLICT	23	23		A -> G (in Ref. 3).	
CONFLICT	256	256		G -> P (in Ref. 2).	
CONFLICT	435	435		F -> L (in Ref. 3).	
CONFLICT	780	780		R -> G (in Ref. 2).	

Sequence information

Length: 1009 Molecular weight: 115875 CRC64: 420B21046274E7C2 [This is a checksum on the AA Da sequence]

```

      10      20      30      40      50      60
MSGVSEPLSR VKLGTLLRRPE GPAEPMVVVP VDVEKEDVRI LKVCFYNSNF NPGKNFKLVK

      70      80      90     100     110     120
CTVQTEIREI ITSILLSGRI GPNIRLAECY GLRLKHKMSD EIHHLHPQMT VGEVQDKYEC

     130     140     150     160     170     180
LHVEAEWRYD LQIRYLPEDF MESLKEDRTT LLYFYQQLRN DYMORYASKV SEGMAQLQGC

     190     200     210     220     230     240
LELRRFFKDM PHNALDKKSN FELLEKEVGL DLFFPKQMQE NLKPKQFRKM IQQTFQQYAS

     250     260     270     280     290     300
LREEECVMKF FNTLAGFANI DQETYRCALI QGWNITVDLV IGPKGIRQLT SQDAKPTCLA

     310     320     330     340     350     360
EFKQIRSIRC LPLEEGQAVL QLGIEGAPQA LSIKTSSLAE AENMADLIDG YCRLQGEHQG

     370     380     390     400     410     420
SLIIHPRKDG EKRNSLPQIP MLNLEARRSH LSESCSIESD IYAEIPDETL RRPGGPQYGI

     430     440     450     460     470     480
AREDVVLNRI LGEGFFGEVY EGVYTNHKGE KINVAVKTC KDCITLDNKEK FMSEAVIMKN

     490     500     510     520     530     540
LDHPIHVKLI GIIEEPTWI IMELYPYGEL GHYLERNKNS LKVLTLVLYS LQICKAMAYL

     550     560     570     580     590     600
ESINCVHRDI AVRNILVASP ECVKLGDFGL SRYIEDEDYY KASVTRLPIK WMSPEINFR

     610     620     630     640     650     660
RFTTASDVWM FAVCMWEILS FGKQPFVLE NKDVIGVLEK GDRLPKPDLC PPVLYTLMTR

     670     680     690     700     710     720
CWDYDPSDRP RFTLVCSLS DVYQMEKDIA MEQERNARYR TPKILEPTAF QEPPPKPSRP

     730     740     750     760     770     780

```

KYRPPPQTNL LAPKLQFQVP EGLCASSPTL TSPMEYPSPV NSLHTPPLHR HNVFKRHSMR

790 800 810 820 830 840
EEDFIQPSSR EEAQQLWEAE KVKMRQILDK QOKQMVEDYQ WLRQEEKSLD PMVYMNDKSP

850 860 870 880 890 900
LTPEKEVGYL EFTGPPQKPP RLGAQSIQPT ANLDRTDDL V LNVMELVRA VLELKNELCQ

910 920 930 940 950 960
LPPEGVYVVV KNVGLTLRKL IGSVDDLPS LPSSSRTEIE GTQKLLNKDL AELINKMRLA

970 980 990 1000
QQNAVTSLSE ECKRQMLTAS HTLAVDAKNL LDAVDQAKVL ANLAHPPAE

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BLAST BLAST submission on
ExPASy/SIB
or at NCBI (USA)



Sequence analysis tools: ProtParam, ProtScale,
Compute pI/Mw, PeptideMass, PeptideCutter,
Dotlet (Java)



ScanProsite, MotifScan



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[\[Features\]](#) [\[Sequence\]](#) [\[Tools\]](#)

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

Entry name **KRAF_CAEEL**
 Primary accession number **Q07292**
 Secondary accession number **Q9N4E3**
 Entered in Swiss-Prot in **Release 30, October 1994**
 Sequence was last modified in **Release 41, February 2003**
 Annotations were last modified in **Release 46, February 2005**

Name and origin of the protein

Protein name **Raf homolog serine/threonine-protein kinase**
 Synonym **EC 2.7.1.37**
 Gene name **Name: lin-45**
 Synonyms: raf-1
 ORFNames: Y73B6A.5
 From **Caenorhabditis elegans [TaxID: 6239]**
 Taxonomy **Eukaryota; Metazoa; Nematoda; Chromadorea; Rhabditida;
 Rhabditoidea; Rhabditidae; Peloderinae; Caenorhabditis.**

References

- [1] NUCLEOTIDE SEQUENCE.
 DOI=10.1038/363133a0;MEDLINE=93247635;PubMed=8483497 [NCBI, ExPASy, EBI, Israel, Japan]
 Han M., Golden A., Han Y., Sternberg P.W.;
 "C. elegans lin-45 raf gene participates in let-60 ras-stimulated vulval differentiation."; *Nature* 363:133-140(1993).
- [2] NUCLEOTIDE SEQUENCE.
 Lee M.-H., Schedl T.;
 "Translation repression by GLD-1 protects its mRNA targets from non-sense mediated mRNA decay."; *Submitted (OCT-2003) to the EMBL/GenBank/DDBJ databases.*
- [3] NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
 STRAIN=Bristol N2;

MEDLINE=99069613;PubMed=9851916 [NCBI, ExPASy, EBI, Israel, Japan]

The C. elegans sequencing consortium;

"Genome sequence of the nematode C. elegans: a platform for investigating biology."; Science 282:2012-2018(1998).

[4] SEQUENCE REVISION.

WormBase consortium;

Submitted (JUN-2001) to the EMBL/GenBank/DDBJ databases.

Comments

- **FUNCTION:** Protein kinase that participates in the induction of C.elegans vulva. Acts downstream of the Ras protein let-60.
- **CATALYTIC ACTIVITY:** ATP + a protein = ADP + a phosphoprotein.
- **COFACTOR:** Binds 2 zinc ions per subunit (*By similarity*).
- **INTERACTION:**
Q17868:cks-1; NbExp=1; IntAct=EBI-314941, EBI-314859;
P34766:pal-1; NbExp=1; IntAct=EBI-314941, EBI-311911;
Q95QC1:r02f2.1; NbExp=1; IntAct=EBI-314941, EBI-331714;
- **SIMILARITY:** Belongs to the Ser/Thr protein kinase family. RAF subfamily.
- **SIMILARITY:** Contains 1 Ras-binding (RBD) domain.
- **SIMILARITY:** Contains 1 zinc-dependent phorbol-ester and DAG binding domain.

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Cross-references

EMBL	L15347; AAA28142.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence]
	AY455928; AAR26307.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence]
	AY493413; AAR86712.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence]
	AC024204; AAF36042.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence]
PIR	S33261; S33261.
HSSP	P35968; 1VR2. [HSSP ENTRY / PDB]
IntAct	Q07292; -.
Ensembl	Y73B6A.5; Caenorhabditis elegans. [Contig view]
WormBase	WBGene00003030; Y73B6A.5.
WormPep	Y73B6A.5; CE25585. [WormPep / WormDB]
InterPro	IPR002219; DAG_PE-bind.
	IPR011009; Kinase_like.
	IPR000719; Prot_kinase.
	IPR003116; RBD.
	IPR008271; Ser_thr_pkin_AS.
Pfam	Graphical view of domain structure.
	PF00130; DAG_PE-bind; 1.
	PF00069; Pkinase; 1.
	PF02196; RBD; 1.
PRINTS	PR00008; DAGPEDOMAIN.
ProDom	PD000001; Prot_kinase; 1.
	[Domain structure / List of seq. sharing at least 1 domain]
SMART	SM00109; C1; 1.

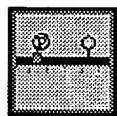
SM00455; RBD; 1.
 PS00479; DAG_PE_BIND_DOM_1; 1.
 PS50081; DAG_PE_BIND_DOM_2; 1.
 PS00107; PROTEIN_KINASE_ATP; 1.
 PS50011; PROTEIN_KINASE_DOM; 1.
 PS00108; PROTEIN_KINASE_ST; 1.
 PS50898; RBD; 1.
 PROSITE graphical view of domain structure.

PROSITE

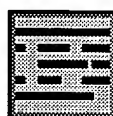
BLOCKS Q07292.
ProtoNet Q07292.
ProtoMap Q07292.
PRESAGE Q07292.
DIP Q07292.
ModBase Q07292.
SMR Q07292; 6376E968D11A9E49.
SWISS-2DPAGE Get region on 2D PAGE.
UniRef View cluster of proteins with at least 50% / 90% identity.

Keywords

ATP-binding; Metal-binding; Phorbol-ester binding; Serine/threonine-protein kinase; Transferase; Zinc.

Features

Feature table viewer



Feature aligner

Key	From	To	Length	Description
DOMAIN	85	161	77	Ras-binding.
DOMAIN	171	217	47	Phorbol-ester and DAG binding.
DOMAIN	481	748	268	Protein kinase.
NP_BIND	487	495	9	ATP (By similarity).
METAL	184	184		Zinc 2 (By similarity).
METAL	187	187		Zinc 2 (By similarity).
METAL	198	198		Zinc 1 (By similarity).
METAL	201	201		Zinc 1 (By similarity).
METAL	206	206		Zinc 2 (By similarity).
METAL	209	209		Zinc 2 (By similarity).
METAL	217	217		Zinc 1 (By similarity).
BINDING	507	507		ATP (By similarity).
ACT_SITE	602	602		Proton acceptor (By similarity).
CONFLICT	801	801		A -> R (in Ref. 1).

Sequence information

Length: 813 Molecular weight: 90407 CRC64: 6376E968D11A9E49 [This is a checksum on the sequence]

AA Da

10	20	30	40	50	60
MSRINFKKSS	ASTTPTSPHC	PSPRLISLPR	CASSSIDRKD	QASPMASPST	PLYPKHSDSL
70	80	90	100	110	120
HSLSGHHSAG	GAGTSDKEPP	KFKYKMIMVH	LPFDQHSRVE	VRPGETARDA	ISKLLKKRNI

```

130      140      150      160      170      180
TPQLCHVNAS SDPKQESIEL SLTMEETIASR LPGNELWVHS EYLNTVSSIK HAIVRRTFIP

190      200      210      220      230      240
PKSCDVCNNP IWMMGFRCEF CQFKFHQRCS SFAPLYCDLL QSVPKNEDLV KELFGIASQV

250      260      270      280      290      300
EGPDRSVAEI VLANLAPTSG QSPAATPDSS HPDLTSIKRT GGVKRHPMAV SPQNETSQLS

310      320      330      340      350      360
PSGPYPRDRS SSAPNINAIN DEATVQHNQR ILDALEAQL EEESRDKTGS LLSTQARHRP

370      380      390      400      410      420
HFQSGHILSG ARMNRLHPLV DCTPLGSNSP SSTCSSPPGG LIGQPTLGQS PNVSGSTTSS

430      440      450      460      470      480
LVA AHLHTLP LTPPQSAPPQ KISPGFFNR SRSPGERLDA QRPRPPQKPH HEDWEILPNE

490      500      510      520      530      540
FIIQYKVGSG SFGTVYRGEF FGTVAIKKLN VVDPTPSQMA AFKNEVAVLK KTRHLNVLLF

550      560      570      580      590      600
MGWVREPEIA IITQWCEGSS LYRHIHVQEP RVEFEMGAI DILKQVSLGM NYLHSKNIIH

610      620      630      640      650      660
RDLKTNNIFL MDDMSTVKIG DFGLATVGTK WTVNGGQQQQ QPTGSILWMA PEVIRMQDDN

670      680      690      700      710      720
PYTPQSDVYS FGICMYEILS SHLPYSNINN RDQILFMVGR GYLRPDRSKI RHDTPKSMMLK

730      740      750      760      770      780
LYDNCIMFDR NERPVFGEVL ERLRDIILPK LTRSQSAPNV LHLD SQYSVM DAVMRSQMLS

790      800      810
WSYIPPATAK TPQSAAAAA ANKKAYYINVY GLI

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13. A method for the modulation of the catalytic activity of a protein kinase, comprising contacting said protein kinase with a compound or salt of claim 1.
14. The method of claim 13, wherein said protein kinase comprises a receptor protein tyrosine kinase.
15. The method of claim 14, wherein said receptor protein tyrosine kinase is selected from the group consisting of EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFR.alpha., PDGFR.beta., CSF1R, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R.
16. The method of claim 13, wherein said protein kinase comprises a non-receptor protein tyrosine kinase.
17. The method of claim 16, wherein said non-receptor protein tyrosine kinase is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes/Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.
18. The method of claim 13, wherein said protein kinase comprises a serine-threonine protein kinase.
19. The method of claim 18, wherein said serine-threonine protein kinase is selected from the group consisting of CDK2 and Raf.

13066118 PMID: 8702470

Tyrosine phosphorylation modulates the activity of clostridial neurotoxins.

Ferrer-Montiel A V; Canaves J M; DasGupta B R; Wilson M C; Montal M
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Journal of biological chemistry (UNITED STATES) Aug 2 1996, 271 (31)
p18322-5, ISSN 0021-9258 Journal Code: 2985121R

Contract/Grant No.: MH48989; MH; NIMH; NS17742; NS; NINDS

Erratum in J Biol Chem 1996 Oct 18;271(42) 26443

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Clostridial neurotoxins' metalloprotease domain selectively cleaves proteins implicated in the process of synaptic vesicle fusion with the plasma membrane and, accordingly, blocks neurotransmitter release into the synaptic cleft. Here we investigate the potential modulation of these neurotoxins by intracellular cascades triggered by environmental signals, which in turn may alter its activity on target substrates. We report that the nonreceptor tyrosine kinase Src phosphorylates botulinum neurotoxins A, B, and E and tetanus neurotoxin. Protein tyrosine phosphorylation of serotypes A and E dramatically increases both their catalytic activity and thermal stability, while dephosphorylation reverses the effect. This suggests that the biologically significant form of the neurotoxins inside neurons is phosphorylated. Indeed, in PC12 cells in which tyrosine kinases such as Src and **PYK2** are highly abundant, stimulation by membrane depolarization in presence of extracellular calcium induces rapid and selective tyrosine phosphorylation of internalized light chain, the metalloprotease domain, of botulinum toxin A. These findings provide a conceptual framework to connect intracellular signaling pathways involving tyrosine kinases, G-proteins, phosphoinositides, and calcium with the action of botulinum neurotoxins in abrogating vesicle fusion and neurosecretion.

Tags: In Vitro; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.

Descriptors: *Botulinum Toxins--metabolism--ME; *Botulinum Toxins--pharmacology--PD; *Membrane Proteins; *Neurotoxins--metabolism--ME; *Neurotoxins--pharmacology--PD; *Tyrosine--metabolism--ME; Animals; Kinetics; Metalloendopeptidases--metabolism--ME; Mice; Nerve Tissue Proteins--metabolism--ME; PC12 Cells; Phosphorylation; Protein-Tyrosine Kinase--metabolism--ME; Rats; Signal Transduction; Substrate Specificity; Synaptic Transmission--drug effects--DE; Synaptic Vesicles--drug effects--DE; src-Family Kinases--metabolism--ME

CAS Registry No.: 0 (Botulinum Toxins); 0 (Membrane Proteins); 0 (Nerve Tissue Proteins); 0 (Neurotoxins); 0 (synaptosomal-associated protein 25); 55520-40-6 (Tyrosine)

Enzyme No.: EC 2.7.1.- (protein tyrosine kinase **PYK2**); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.1.112 (src-Family Kinases); EC 3.4.24 (Metalloendopeptidases)

Record Date Created: 19960924

Record Date Completed: 19960924

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L14: Entry 21 of 33

File: USPT

May 23, 2000

US-PAT-NO: 6066463

DOCUMENT-IDENTIFIER: US 6066463 A

TITLE: Method and compositions for treatment of BCR-ABL associated leukemias and other cell proliferative disorders

DATE-ISSUED: May 23, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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US-CL-CURRENT: 435/7.23; 435/7.1, 435/7.2, 435/7.24, 436/63, 436/64

CLAIMS :

What is claimed is:

1. A method for identifying a compound to be tested for an ability to modulate a cell proliferative disorder involving a protein tyrosine kinase polypeptide/GRB-2 adaptor polypeptide complex comprising:

(a) contacting a cell that forms a complex comprising a GRB-2 adaptor polypeptide SH2- or SH3-binding portion of the protein tyrosine kinase polypeptide and an SH2 or SH3 portion of the GRB-2 adaptor polypeptide with the compound for a time sufficient to allow intracellular binding of the compound to the complex or at least one of the polypeptides;

(b) detecting the level of the complex present in the cell of step (a); and

(c) comparing the level of the complex detected in step (b) to the level of complex present in a cell of the type in step (a) that has not contacted the compound, so that if the level detected in step (b) is less than the level present in a cell that has not been contacted with the compound, a compound to be tested for an ability to modulate a cell proliferative disorder involving a protein tyrosine kinase polypeptide/GRB-2 adaptor polypeptide complex is identified.

2. The method of claim 1 wherein the protein tyrosine kinase polypeptide of the the protein tyrosine kinase/GRB-2 adaptor polypeptide complex is a transmembrane, receptor protein tyrosine kinase polypeptide.

3. The method of claim 1 wherein the protein tyrosine kinase polypeptide of the the protein tyrosine kinase/GRB-2 adaptor polypeptide complex is an intracellular, cytoplasmic protein tyrosine kinase polypeptide.

4. The method of claim 3 wherein the intracellular, cytoplasmic protein



US006066463A

United States Patent [19]
Schlessinger et al.

[11] **Patent Number:** **6,066,463**
 [45] **Date of Patent:** **May 23, 2000**

- [54] **METHOD AND COMPOSITIONS FOR TREATMENT OF BCR-ABL ASSOCIATED LEUKEMIAS AND OTHER CELL PROLIFERATIVE DISORDERS**
- [75] **Inventors:** Joseph Schlessinger, New York, N.Y.; Mikhail L. Gishlitzky, Palo Alto, Calif.; Ann Marie Pendergast, Durham, N.C.
- [73] **Assignees:** New York University, New York, N.Y.; Duke University, Durham, N.C.; Sugen, Inc., South San Francisco, Calif.

- [21] **Appl. No.:** 08/246,441
 [22] **Filed:** May 20, 1994

Related U.S. Application Data

- [63] Continuation-in-part of application No. 08/127,922, Sep. 28, 1993, abandoned.
- [51] **Int. Cl.⁷** G01N 33/574; G01N 33/53; G01N 33/48
- [52] **U.S. Cl.** 435/7.23; 435/7.24; 435/7.2; 435/7.1; 436/63; 436/64
- [58] **Field of Search** 435/7.23, 7.24; 424/9.2, 138.1; 436/63, 64

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(List continued on next page.)

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Attorney, Agent, or Firm—Pennie & Edmonds LLP

[57] ABSTRACT

The present invention relates to compositions and methods for the prevention and treatment of cell proliferative disorders wherein a protein tyrosine kinase or protein tyrosine phosphatase capable of complexing with a member of the SH2- and/or SH3-containing family of adaptor proteins is involved. This invention is based, in part, on the surprising discovery that the adaptor protein, GRB-2, binds the intracellular BCR-ABL tyrosine kinase product *in vivo* and is necessary for the activation of the oncogenic potential of the BCR/ABL product. The present invention further relates to protein tyrosine kinase/adaptor protein complexes and the uses of these complexes for the identification of agents capable of decreasing or inhibiting the interaction between the members of such complexes.

18 Claims, 20 Drawing Sheets